REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 5-12 are pending in the present application. Support for claims 5-12 may be found in original claims 1-4 and in the present specification at page 1, lines 1-3 and page 3, lines 17-19. Claims 1-4 have been canceled.

In the outstanding Official Action, the Official Action states that the BOISMARE et al. publication had not been considered. However, the Examiner's attention is respectfully directed to MPEP §609(a)(e), which states that when the information listed in an Information Disclosure Statement is not in the English language, but was cited in a search report or other action by a foreign patent office in a counterpart foreign application, the requirement for a concise explanation of relevance can be satisfied by submitting an English-language version of the search report or action which indicates the degree of relevance found by the foreign office. This may be an explanation of which portion of the reference is particularly relevant, to which claims it applies, or merely an "X", "Y", or "A" indication on the search report.

At this time, the Examiner's attention is respectfully directed to the Information Disclosure Statement filed with the

present application on April 4, 2004. The Information Disclosure Statement includes an English-language version of the search report or action that indicates the degree of relevance found by the foreign office that conducted the search. Thus, applicants believe that the Information Disclosure Statement satisfies the requirements for a concise explanation pursuant to MPEP §609(a)(3). As a result, applicants respectfully request that the BOISMARE et al. publication be considered.

In the outstanding Official Action, claim 3 was rejected for allegedly not satisfying the requirements of 35 USC 112, second paragraph and 35 USC 101. However, as noted above, claim 3 has been canceled. As a result, applicants believe that the present amendment obviates this rejection.

In the outstanding Official Action, claims 3-4 were rejected under 35 USC 102(b) as allegedly being anticipated by BRUINVELS et al. This rejection is respectfully traversed.

Applicants believe that BRUINVELS et al. fail to anticipate or render obvious the claimed invention. As the Examiner is aware, to constitute anticipation, all material elements of the claim must be found in one prior art source, which must be enabling to one skilled in the art, i.e., enable that person to understand the nature and operation of the invention. *Seymore vs. Osborne*, 78 U.S. 516 (USSC 1870); *In re Spada*, 911 F.2d 705, 15 U.S.P.Q. 2d 1655 (Fed. Circ. 1990). Upon reviewing the BRUINVELS et al. patent, applicants believe that

the BRUINVELS et al. patent fails to qualify as an enabling publication.

The BRUINVELS et al. patent pertains to the finding that baclofen may be effective in the treatment of anxiety neurosis (nowadays, generalized as anxiety disorders and panic attacks). Patients described by BRUINVELS et al. are individuals suffering from this type of anxiety. Baclofen is reported to ameliorate the symptoms of this type of anxiety.

Applicants do not believe that BRUINVELS et al. enable one skilled in the art to treat alcoholics. According to the Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition (DSM-IV), anxiety disorders and alcoholism are two separate and distinct mental disorders. They are classified by completely independent diagnostic criteria. Specifically, anxiety disorders are defined as follows:

> Generalized anxiety disorders
>
> For more than half the days in at least six months, the patient experiences excessive anxiety and worry about several events or activities. The patient has trouble controlling these feelings. Associated with this anxiety and worry, the patient has three or more of the following symptoms, some of which are present for over half the days in the past six months: feels restless, edgy, keyed up; tires easily; trouble concentrating; irritability; increased muscle tension;

trouble sleeping (initial insomnia or restless, unrefreshing sleep). The symptoms cause clinically important distress or impair work, social or personal functioning.

Panic attacks

The patent suddenly develops a severe fear or discomfort that peaks within 10 minutes. During this discrete episode, four or more of the following symptoms occur: chest pain or other chest discomfort, chills or hot flashes; choking sensation; derealization (feeling unreal) or depersonalization (feeling detached from self); dizzy, lightheaded, faint or unsteady; fear of dying; fears of loss of control or becoming insane; heart pounds, races or skips beats; nausea or other abdominal discomfort; numbness or tingling; sweating; shortness of breath or smothering sensation; trembling.

Alcoholism (which includes both alcohol dependence and alcohol abuse) is a multifaceted disease, with a complex etiology and made of multiple, complex psychiatric and neurological components (loss of control, relapse, withdrawal syndrome). DSM-IV defines alcoholism as follows:

Alcohol dependence

The patient's maladaptive pattern of alcohol use leads to clinically important distress or impairment

as shown in a single 12-month period by three or more of the following: tolerance, shown by either of markedly increased intake of the alcohol is needed to achieve the same effect or, with continued use, the same amount of the alcohol has markedly less effect; withdrawal, shown by either of the alcohol's characteristic withdrawal syndrome or the alcohol (or one closely related) is used to avoid or relieve withdrawal symptoms; the amount of duration of use is often greater than intended; the patient repeatedly tries without success to control or reduce alcohol use; the patient spends much time using the alcohol, recovering from its effects or trying to obtain it; the patient reduces or abandons important social, occupational or recreational activities because of alcohol use; the patient continues to use the alcohol, despite knowing that it has probably caused physical or psychological problems.

Alcohol abuse

The patient's maladaptive alcohol use pattern causes clinically important distress or impairment as shown in a single 12-month period by one or more of the following: because of repeated use, the patient fails to carry out major obligations at work or at home; the patient uses alcohol even when it is

physically dangerous; the patient repeatedly has legal problems from alcohol use; despite knowing that it has caused or worsened social or interpersonal problems, the patient continues to use the alcohol.

As can be seen, there is no mention of anxiety among the criteria required for the diagnosis of alcoholism. While the patients of the study of BRUINVELS et al. may have consumed alcohol, they were given baclofen to cure anxiety. It is believed that the data provided by BRUINVELS et al. does not suggest that baclofen was curing alcoholism.

In other words, the incidental observation made by BRUINVELS et al. would not lead to a reasonable expectation of success of obtaining the claimed invention. Indeed, this conclusion is supported by "historical evidence": since 1979, no study has ever investigated the effectiveness of baclofen in the treatment of alcoholism. Moreover, since 1979, BRUINVELS and his research group have published no studies that examine the supposed beneficial effect of treatment with baclofen on alcohol dependence (see the list of papers by BRUINVELS attached with this amendment in the appendix).

Indeed, upon reviewing the BRUINVELS et al. patent, applicants believe that BRUINVELS et al. actually teach away from the claimed invention. At column 2, lines 23-27, BRUINVELS et al. state that it was known that several patients suffering from anxiety neurosis resorted to an excessive use of alcohol, often

followed by chronic alcohol misuse. In particular, BRUINVELS et al. state that "apparently the alcohol was the only drug that helped up till now". Thus, BRUINVELS et al. discuss alcohol in terms of a drug that patients suffering from such anxiety disorders used to alleviate their anxiety. BRUINVELS et al. do not teach that baclofen or a stereoisomer thereof would be effective in treating alcoholism.

Thus, applicants believe that the BRUINVELS et al. patent fails to qualify as enabling publication. As a result, applicants believe that BRUINVELS et al. fails to anticipate the claimed invention.

Claims 3-4 were rejected under 35 USC 102(b) as allegedly being anticipated by ROBSON et al.

Applicants believe that ROBSON et al. fails to disclose or suggest the claimed invention. ROBSON et al. provide experimental results demonstrating that baclofen treatment may a) ameliorate the severity of morphine withdrawal syndrome in monkeys, and b) reduce morphine self-administration in rats trained to press a lever to self-administer morphine. However, an extension to alcohol and barbiturates is not supported by the disclosure of ROBSON et al. Opioids (e.g., morphine), barbiturates and alcohol possess different mechanisms of action and pharmacological profiles; more specifically, with regard to the issue raised by ROBSON et al., dependence by morphine (or

heroin), barbiturates and alcohol are phenomena with different neurobiological bases and therapeutic approaches.

For example, methadone is the drug of choice in the treatment of heroin addiction. However, it has been found to stimulate voluntary alcohol intake in rats (MUDAR P.J., LeCANN N.C., CZIRR S.A., HUBBELL C.L., REID L.D. Methadone, pentobarbital, pimozide and ethanol intake. Alcohol 1986; 3(5):303-8. See the abstract in the Appendix). As a further example, the opioid receptor antagonists, naloxone and naltrexone, dramatically potentiate opioid withdrawal syndrome, while they are ineffective on alcohol withdrawal syndrome. In conclusion, any theoretical generalization from opioid dependence to alcohol dependence is not supported by experimental evidence. As a result, applicants do not believe that ROBSON et al. enables one skilled in the art to practice the claimed method.

Thus, in view of the above, applicants believe that ROBSON et al. fails to anticipate or render obvious the claimed invention.

In the outstanding Official Action, claim 4 is rejected under 35 USC 102(b) as allegedly being anticipated by XP-001036625 or KREUTNER et al. However, as noted above, claim 4 has been canceled. Claim 4 was directed to a pharmaceutical composition. As claims 5-12 are directed to method claims, applicants believe that these rejections have been obviated by the present amendment.

Claim 3 was rejected under 35 USC 103(a) as allegedly being unpatentable over XP-001036625. This rejection is respectfully traversed.

Applicants believe that the XP-001036625 publication fails to render obvious the claimed invention. Applicants do not believe that the publication enables one skilled in the art to practice the claimed invention.

The effect of baclofen on some alcohol-induced responses, including alcohol withdrawal syndrome, did not enable one skilled in the art to practice the claimed invention or provide a reasonable expectation of success at the time the application was filed. Indeed, studies at the time the application was filed did not disclose or suggest the use of baclofen to treat alcoholism. Indeed, the studies were contradictory and surely not conclusive. Baclofen had been found to a) alleviate (File SE, ZHARKOVSKY A., GULATI K. Effects of baclofen and nitrendipine on ethanol withdrawal responses in the rat, Neuropharmacology 1991; 30:183-190), b) have no effect on (HUMENIUK R.E., WHITE J.M., ONG J. The effects of $GABA_B$ ligands on alcohol withdrawal in mice. Pharmacol, Biochem. Behav. 1994; 49;561-566; see abstract in Appendix), or c) even potentiate (HUMENIAK et al., 1994; see abstract in Appendix) different signs of alcohol withdrawal syndrome in alcohol-dependent rats and mice.

Because of the striking discrepancies, applicants believe that the publication fails to qualify as an enabling publication.

In view of the present amendment and foregoing Remarks, therefore, applicants believe that the present application is in condition for allowance at the time of the next Official Action. Allowance and passage to issue on that basis is respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item(s):

☐ - a terminal disclaimer

☐ - a 37 CFR 1.132 Declaration

☐ - a new or amended Abstract of the Disclosure

☐ - a Replacement Sheet for Figure of the drawings

☐ - a Substitute Specification and a marked-up copy of the originally-filed specification

☐ - a verified English translation of foreign priority document

☒ - List of papers reporting the results of clinical studies published by BRUINVELS and co-workers in peer-reviewed journals from 1979 to today

☒ - MUDAR P.J., LeCANN N.C., CZIRR S.A., HUBBELL C.L., REID L.D. Methadone, pentobarbital, pimozide and ethanol intake. Alcohol 1986; 3(5):303-8. Abstract

☒ - HUMENIUK R.E., WHITE J.M., Ong J. The effects of $GABA_B$ ligands on alcohol withdrawal in mice. Pharmacol Biochem Behav. 1994 Nov;49(3):561-6. Abstract

List of papers reporting the results of clinical studies published by Bruinvels and co-workers in peer-reviewed journals from 1979 to today:

Fekkes D, Pepplinkhuizen L, Verheij R, Bruinvels J. Abnormal plasma levels of serine, methionine, and taurine in transient acute polymorphic psychosis. Psychiatry Res. 1994; 51:11-18.

Fekkes D, Schouten MJ, Pepplinkhuizen L, Bruinvels J, Lauwers W, Brinkman UA. Norharman, a normal body constituent. Lancet 1992; 339:506.

Fekkes D, Pepplinkhuizen L, Bruinvels J. Changes in serine metabolism by a serum factor present in a group of episodic psychotic patients. Biol. Psychiatry 1991; 30:966-972.

Bruinvels J, Pepplinkhuizen L, Fekkes D. Derangement of one-carbon metabolism in episodic schizoaffective psychoses. Pharmacopsychiatry 1988; 21:28-32.

Fekkes D, Bruinvels J. Serine and folate metabolism in fibroblasts from episodic psychotic patients with psychedelic symptoms. Biol. Psychiatry 1986; 21:951-959.

Wunderink A, Pepplinkhuizen L, Bruinvels J. Nutrition and psychoses. Prog. Brain Res. 1986; 65:49-57.

Bruinvels J, Pepplinkhuizen L. Serine, glycine and carbohydrates in schizoaffective disorders. Bibl. Nutr. Dieta 1986; 38:168-172.

Bruinvels J, Pepplinkhuizen L. Impaired glycine-serine conversion and increased plasma taurine levels in episodic psychotic patients with psychedelic symptoms. J. Psychiatr. Res. 1984; 18:307-318.

Pepplinkhuizen L, Bruinvels J, Blom W, Moleman P. Schizophrenia-like psychosis caused by a metabolic disorder. Lancet 1980; 1:454-456.

Mudar PJ, LeCann NC, Czirr SA, Hubbell CL, Reid LD. Methadone, pentobarbital, pimozide and ethanol-intake. Alcohol 1986;3(5):303-8. Abstract: For 28 days, water-deprived rats were given a daily, 1-hr opportunity to take a sweetened ethanol solution (ES) or water. Across days under this regimen, rats gained weight normally and increased intake of ES until they were taking considerable amounts. Across the next 13 days of the regimen, selected groups were given, before the opportunity to drink, one of five doses of methadone (from 0.5 to 8.0 mg/kg), pentobarbital (from 5 to 30 mg/kg), or their vehicles. Large doses of both agents increased intakes, with methadone (1 and 2 mg/kg) increasing only ES-intake. Subsequently, while the daily regimen continued, rats were given pimozide (0.2, 0.4, or 0.6 mg/kg) at either 1 or 4 hr before the opportunity to drink. Pimozide did not reduce ES-intake. Next, they were given a dose of pentobarbital (5.0 mg/kg) with challenge doses of naloxone (0.3, 1.0, 3.0 mg/kg). Naloxone dose-relatedly antagonized pentobarbital's potential to increase intakes.

Humeniuk RE, White JM, Ong J. The effects of $GABA_B$ ligands on alcohol withdrawal in mice. Pharmacol Biochem Behav. 1994 Nov;49(3):561-6. Abstract: Recent research suggests that the $GABA_B$ receptor may mediate some of the acute effects of alcohol, but little is known of its involvement in alcohol withdrawal. Mice made dependent on alcohol exhibited tremor and tail arch when consumption ceased. Diazepam dose-dependently attenuated both tremor and tail arch, whereas baclofen had no effect on either of these two withdrawal symptoms. However, baclofen dose-dependently induced convulsant behaviour in the withdrawing mice, and this was significantly attenuated by the $GABA_B$ antagonists phaclofen (50 mg/kg) and CGP 35348 (300 mg/kg), but not BPBA (50 mg/kg). Phaclofen, BPBA, and CGP 35348, when administered alone and in combination with a single dose of baclofen, did have an effect on tremor, although the magnitude was small in comparison to that seen with diazepam. It appears that the $GABA_B$ receptor may play a role in mediating convulsions during alcohol withdrawal, and that in this system baclofen is proconvulsant.